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# Sulthiame add-on therapy in children with Lennox-Gastaut syndrome: A study of 44 patients

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ABSTRACT

*Purpose:* The aim of this study was to evaluate efficacy and tolerability of sulthiame as an add-on treatment in 44 patients with Lennox-Gastaut syndrome (LGS) refractory to other antiepileptic drugs and/or non-pharmacological treatment.

*Methods:* Patients were selected according to the following criteria: (1) age 4 years or older, (2) a diagnosis of LGS refractory to at least four previous antiepileptic drugs, alone or in combination.

Neurologic examinations, brain magnetic resonance imaging, and repeated prolonged electroencephalography (EEG) or video-EEG studies were performed in all cases. Data on school achievements and/or neuropsychological evaluations were obtained during the follow-up of 1–3 years. Sulthiame was added in doses ranging from 5 to 30 mg/kg/day.

*Results:* Twenty-seven of 44 patients (61%) who received sulthiame as add-on therapy had a greater than 50% seizure decrease after a mean follow-up period of 20 months. Complete seizure freedom was achieved in one patient (2%). Four patients (9%) had a 25–50% seizure decrease, while seizure frequency remained unchanged in 12 (25%), and was increased in one (2%). Hyperpnoea and dyspnoea were observed in four patients, and nausea, drowsiness, and headache were seen in one patient each; however, these manifestations were transient and discontinuation of sulthiame was not necessary. Two other patients had decreased appetite, skin rash, and irritability. The adverse effects were mild and transient in these nine cases.

*Conclusion:* Sulthiame as an adjunctive therapy achieved a more than 50% seizure reduction in 27 of 44 patients with LGS with only mild or moderate adverse effects.

## 1. Introduction

Lennox-Gastaut syndrome (LGS) is a paediatric epilepsy syndrome described as a triad consisting of multiple seizure types, such as tonic –mostly occurring at night–, atonic, and atypical absence seizures, intellectual disability or regression, and abnormal electroencephalography (EEG) findings with a symptom onset before 12–24 months of age [1]. The EEG abnormalities consist primarily of an interictal pattern of diffuse, slow spike-wave complexes at 2.5 Hz during wakefulness and paroxysmal fast rhythms (10–20 Hz) during sleep, mainly in the non-rapid eye movement phase, which is the hallmark of tonic seizures [1].

There is no biological marker for LGS and its aetiology may be genetic, structural, or of unknown cause in around 25–30% of the cases [2,3].

Valproic acid is still considered as the first-line treatment for patients with *de novo* LGS. If ineffective, clobazam, lamotrigine or rufinamide may be added as adjunctive therapy. If seizure control remains inadequate, the choice of the next adjunctive antiepileptic drug (AED) should be evaluated for each case [3].

AEDs can be used together with non-pharmacological therapies, including the ketogenic diet (KD), callosotomy, and vagus nerve stimulation (VNS). The KD has been found to work particularly well in patients with LGS of unknown cause [4]. Recently, cannabidiol has been shown to be effective as an adjunctive therapy in LGS patients [5].

Sulthiame (STM) acts as a membrane-permeant carbonic anhydrase

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inhibitor with a beneficial effect on epileptiform activity, which results, at least in part, from a modest intracellular acidosis of central neurons [6]. STM has also been shown to inhibit voltage-gated sodium channels [6].

In the 1980s, the German child neurologist Hermann Doose found STM to be effective in benign focal epilepsies of childhood [7] and since then the drug has been used in sporadic cases [8,9]. Subsequently, STM was used in epileptic encephalopathies with continuous spikes and waves [10].

LGS is one of the childhood epileptic encephalopathies known to be particularly refractory to AEDs and non-pharmacological therapies. Based on the efficacy of STM in focal as well as other types of seizures, in 2010 our group started to use the drug in patients with refractory LSG.

The aim of this study was to evaluate efficacy and tolerability of STM as add-on treatment in 44 patients with LGS, who were refractory to other AEDs and/or non-pharmacological treatment.

## 2. Material and methods

Medical records of 53 patients with LGS treated with add-on STM seen at six paediatric neurology centres in Argentina between May 2015 and March 2018 were retrospectively analysed. The patients were enrolled at each centre on an intention-to-treat basis and entered into their respective databases.

Inclusion criteria were: (1) age 4 years or older, and (2) a diagnosis of LGS refractory to at least four previous AEDs, alone or in combination. Informed consent was obtained from the parents and/or caregivers of all the patients. The study was approved by the Institutional Review Board of each centre.

Exclusion criteria were other epileptic encephalopathies (e.g., epileptic encephalopathy with continuous spikes and waves) and focal epilepsy with secondary bilateral synchrony that did not fulfil criteria for LGS, as well as progressive neurological or systemic disease. Patients with abnormal liver, kidney, or blood laboratory tests were also excluded.

The diagnosis of LGS was made based on the ILAE classification considering polymorphous seizures including tonic–axial, atonic, and absence seizures, as well as other seizure types such as myoclonic, generalized tonic–clonic, or partial seizures, (2) abnormal background activity, slow spike-wave discharges, and episodic fast activity during sleep on the EEG, and (3) intellectual disability [11,12].

The parents and/or caregivers had kept an epilepsy diary to record seizures occurring at home and at school. At each follow-up visit, seizure frequency, type, and duration were evaluated. The seizures were classified according to the International League against Epilepsy Revised Classification of Seizures [13,14]. Improvements on the EEG was evaluated by the treating neurologist based on a more or less than 50% reduction of the slow spike-waves, diffuse fast rhythms, and multifocal spikes, mainly during the maximum sleep stage on a video-EEG recording of at least 2 h. EEG abnormalities were quantitatively assessed before and after STM initiation; however, due to the retrospective nature of the study, no systematic mathematical and statistical analysis could be performed [15].

All patients had received more than four other AEDs before STM was added in doses ranging from 5 to 30 mg/kg/day. STM was titrated over a period of 3 to 8 weeks starting at a dose of 100 mg/day up to a maximum dose of 800 mg/day. The average STM dose was 20 mg/kg/day in patients with a structural and 15 mg/kg/day in patients with an unknown aetiology. The dose was established based on the initial clinical and EEG response and tolerability. After STM initiation, concomitant AEDs were not modified and no other AEDs were started. In the 16 patients with VNS, setting parameters remained unchanged.

Efficacy was assessed by comparing seizure frequency before and after initiating STM therapy. Response to treatment was defined as (1) seizure freedom, (2) a 50%–99% decrease in seizure frequency, (3) a 25%–50% decrease in seizure frequency, (4) increase in seizure frequency, and (5) no change.

Computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed in all patients. Brain MRIs were performed with a General Electric Sigma Horizon LX, 1.5 T equipment (General Electric, Milwaukee, WI, USA). EEG and Video-EEG were repeated several times a year according to the evolution of the patients. Data on school achievements and neuropsychological evaluations (Terman & Merrill, or WISC III or IV) were obtained during the follow-up.

Blood chemistry and liver and kidney function were carefully assessed before STM was introduced and during the follow-up period. Molecular biology studies were not performed.

For statistical analysis the two-tailed Wilcoxon rank-sum and the Fisher exact tests were used and a $p < 0.05$ was considered significant.

## 3. Results

### 3.1. General characteristics

We evaluated 44 patients (28 males, 16 females), aged between 4 and 16 years with a mean and median age of 9 and 10 years, respectively. The patients were treated with STM for a mean period of 20 months (range, 12–60 months).

Fifteen patients were diagnosed as having an unknown aetiology and 29 as structural LGS. Of the latter patients, 12 had malformations of cortical development, 11 brain atrophy, three tuberous sclerosis, and three others encephalitis. All patients had intellectual disability, which was found to be mild in 10, moderate in 19, and severe in 15.

CT scan and MRI showed abnormal findings in 29/44 patients (66%); brain atrophy was observed in 11, brain malformations in 12, tuberous sclerosis in three, and a **destructive** lesion in three others.

Mean and median age at seizure onset was 2.5 and 3 years, respectively. Mean duration of epilepsy was 4 years. Seizure types observed before STM initiation were atypical absences in 15 (34%), atonic and/or myoclonic seizures in 37 (82%), tonic seizures in 35 (76%), focal seizures in 20 (45%), and tonic-clonic seizures in 15 patients (34%). Before STM initiation, the patients had a mean of 13 seizures per day (range, 2–26).

All patients had received more than four AEDs before STM was added, in doses ranging from 10 to 35 mg/kg/day. The mean number of AEDs tried before STM was 8.5. The mean STM dose was 25 mg/kg/day. The mean and median number of concomitant AEDs was 2.5 and 2, respectively. Concomitant AEDs were valproic acid in 80%, levetiracetam in 66%, clobazam in 34%, topiramate in 34%, rufinamide in 34%, and lamotrigine in 23%. Four (9%) and 16 (36%) patients were on the KD or VNS, respectively.

### 3.2. Efficacy

Twenty-seven of 44 patients (61%) who received STM as add-on therapy had a greater than 50% decrease in seizures after a mean follow-up of 20 months. One patient (2%) became seizure free. Four patients (9%) had a 25–50% seizure reduction, while seizure frequency remained unchanged in 11 (23%) and increased in one patient (2%).

Considering seizure type, 21 of the 27 responders (78%) had a greater than 50% reduction in drop attacks (atonic and/or myoclonic seizures), 17/27 (63%) had a greater than 50% decrease in tonic seizures, 9/27 (33%) had a greater than 50% decrease in atypical absences, 6/27 had a greater than 50% decrease in focal, and 6/27 others had a greater than 50% decrease in generalized tonic-clonic seizures.

No statistical difference was found between responders and non-responders regarding age at seizure onset, epilepsy duration, and age at STM initiation. When evaluating the patients with a greater than 50% decrease in seizure frequency, there was no difference between the patients with an unknown aetiology and those with a structural aetiology. A better control of the drop attacks was seen in the patients

with an unknown aetiology compared to those with a structural aetiology, although this difference was not statistically significant.

Sixteen patients with LGS (11 with a structural and five with an unknown aetiology) had undergone implantation of a VNS device and one callosotomy previous to STM initiation with no significant reduction in seizure frequency. On STM, nine of the patients with VNS showed a greater than 50% decrease in drop attacks and tonic seizures after a mean follow-up period of 20 months. Two patients had been receiving the KD with only a partial response. When STM was added, one of these patients had a greater than 50% decrease in seizures.

No correlation was found between number of prior or concomitant AEDs or non-pharmacological treatment and outcome.

In all patients with a greater than 50% seizure decrease, slow spike-and-waves, diffuse fast rhythms, and multifocal spikes on the interictal EEG improved more than 70%, 65%, and 60%, respectively. In the patient with an unknown aetiology who became seizure free, the EEG normalized.

### 3.3. Adverse effects

Adverse effects were observed in 10 patients. Four patients had hyperpnoea and dyspnoea and nausea, drowsiness, and headache were seen in one patient each; however, these manifestations were transient and did not lead to the need to discontinue STM. Two other patients had decreased appetite, allergic skin rash, and irritability. These adverse effects were also transient and mild in all nine cases. Laboratory tests were normal in all patients, except in four patients who had hyperpnoea and dyspnoea associated with mild metabolic alkalosis. In these cases, decrease of the STM dose resolved the alteration.

In only one patient with a structural aetiology, the seizures worsened and STM was discontinued.

Blood levels of concomitant anticonvulsant drugs were not modified by the addition of STM.

### 3.4. Follow-up

Over a mean follow-up of 20 months, efficacy of STM was maintained in 27/44 patients who had a greater than 50% decrease in seizures. The only patient who became seizure free did not have any other seizures during the follow-up period.

## 4. Discussion

In this retrospective study of 44 children with LGS who received STM as add-on treatment, the drug showed good efficacy and tolerability over a sufficiently long follow-up period. To our knowledge, our study reports the largest number of patients with LGS treated with STM after failing to respond to other AEDs and non-pharmacological treatment.

In this series, STM was found to reduce overall seizure frequency by more than 50% in 61% of patients with LGS who were refractory to at least four previous antiepileptic drugs. Drop attacks and tonic seizures and, to a lesser extent, atypical absences and tonic–clonic and focal seizures best responded to the drug. Additionally, a trend toward a better response to STM for drop attacks was seen in patients with an unknown aetiology.

In our patient with an unknown aetiology who became seizure free, the EEG normalized and in those who had a $\geq$50% seizure reduction, the EEG abnormalities improved significantly. In a placebo-controlled trial evaluating the effect of STM on the EEG in children with benign childhood epilepsy with centrotemporal spikes (BECTS), a marked decrease of interictal epileptiform activity was observed [15].

Additionally, a randomized controlled trial in 43 children with BECTS treated with either STM or levetiracetam showed a prompt, sustained, and statistically significant response on the EEG. Persistent EEG abnormalities were associated with treatment failure [16].

In our series, one patient out of 44 (2%) had an increase in seizures. Seizure worsening on STM has not been shown in other studies, although such a possibility cannot be ruled out and further studies to evaluate the drug are necessary.

Regarding tolerability, severe adverse effects to STM have not been reported so far. In our series, adverse effects probably linked to STM were observed in 22% of the patients. They mainly consisted of hyperpnoea, drowsiness, and loss of appetite. In none of the patients these adverse effects led to the need to withdraw STM. Nevertheless, the number of patients in this study is too small to draw any definite conclusions.

Currently, there has been renewed interest in other potential uses for STM, e.g. in West syndrome and other refractory epilepsies [7]. Over the past years, it has been shown that STM may be useful in the treatment of refractory myoclonic epilepsies, including progressive myoclonic epilepsy [2]. One isolated case with LGS was treated with STM [8].

In a 2013 Cochrane review assessing AED treatment for LGS, the authors concluded that optimum treatment for LGS remains uncertain and that no drug appears highly efficacious. Rufinamide, lamotrigine, topiramate and felbamate were considered to be helpful as add-on therapy and clobazam for drop attacks [17]. A second Cochrane review evaluating the efficacy and adverse-effect profile of STM as monotherapy when compared with placebo or another antiepileptic drug was unable to draw any meaningful conclusions [18]. A subsequent review evaluating STM add-on therapy, while observing that the drug may lead to a cessation of seizures when used as an add-on therapy to pyridoxine in patients with West syndrome, found no evidence for the use of STM as an add-on therapy in patients with epilepsy [19].

As for all types of epilepsy, polytherapy (AEDs) and comorbidity-associated medications should be rationalized and minimized whenever possible. The rationale for specific AEDs should be considered routinely as part of patient re-evaluation. In addition, clinicians should proactively ask the patient/parent/caregiver about AEs and not expect spontaneous reporting [3].

Recently, in an expert opinion on the management of LGS a treatment algorithm and practical considerations have been published. The proposal considers a first-line pharmacological therapy, adjunctive therapy, second-line adjunctive therapy, and subsequent adjunctive therapies consisting of AEDs that have not been approved for use in LGS as well as non-pharmacological therapy [3]. In cases with LGS associated with a focal or unilateral lesion, resective surgery and in those with unknown aetiology the KD should be evaluated as early treatment options [3]. Although currently an off-label drug for the management of LGS, we believe that STM should be subsequently considered in the treatment scheme.

LGS is one of the severe, treatment-resistant epileptic encephalopathies. The high seizure frequency and the drop attacks associated with the risk of trauma affect the quality of life of the patients and their families.

Currently, evidence on therapeutic strategies for LGS is lacking and observational studies based on individual patient characteristics are needed [20]. As in spite of different management options many cases still fail to respond to therapy, we decided to evaluate STM in this series of treatment-resistant patients. The results of this study may be a useful contribution considering the relative paucity of data on the use of STM in LGS. Epileptologists may be encouraged to corroborate our findings in their management of patients with LGS.

## 5. Conclusion

In this study STM reduced seizure frequency in children and adolescents with LGS. The drug showed to be particularly effective against myoclonic-atonic seizures and tonic seizures. Atypical absence seizures, myoclonic seizures, focal and generalized tonic-clonic were also reduced. STM was generally well tolerated.

Further experience is warranted to gain a better understanding of the efficacy of STM in the long-term follow-up.

## Declarations of interest

None.

## Conflict of interest

We have no financial and personal relationships with other people or organizations to disclose that could inappropiately influence this work.

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